REMARKS

Applicants now respond to the Office Action of February 21, 2003. Claims 32-49 are currently pending. Claims 32, 35-38, 41-44, and 47-49 have been amended to consistently use the term "wherein" rather than "in which" in the claim language. No new matter is added.

Restriction Requirement

The Office checked box 8 on the Office Action Summary indicating that claims 32-49 are subject to restriction and/or election requirement. However, the comments following the Office Action Summary did not include any description of a restriction requirement or discussion of a required election. For the purpose of this response, the applicants assume the examiner intended to check box 6, indicating that claims 32-49 are rejected.

Claim Rejections - 35 U.S.C. § 103

The Office rejected claims 32-49 under 35 U.S.C. §103 as being unpatentable over the Rooke et al. patent, WO91/15197, G.B. 2,005,538H, Ruberto et al., Feldman et al., Jacobsson et al., and Arguedas et al. references, all of record taken together.

The Applicants acknowledge that these references have been cited previously by the Office in the parent application. The Applicants respectfully submit that the Office has not established a *prima facie* case of obviousness.

As is well recognized, the *prima facie* case has three requirements (MPEP § 2143), and the present rejection does not satisfy any of these requirements. Specifically, the references, separately or combined, do not supply any motivation to modify the teachings to arrive at the claimed invention. Nor do the combined references convey any reasonable expectation of success. Finally, even if modified or combined as proposed, the resultant modification would still fall short of yielding the combined invention. Applicants refer the Office to the previous arguments submitted in the responses dated April 6, 2001, and January 11, 2002, submitted in the parent and instant applications. In requesting reconsideration of a *prima facie* finding of obviousness, Applicants submit expanded legal arguments.

As described previously, the present invention is directed to a method of treating bacterial infections in a pediatric patient wherein the formulation is administered in a dosage amount of 45 ± 10% mg/kg of amoxycillin and 6.4 ± 10% mg/kg of clavulanate in divided

doses twice daily. In a further aspect, the present invention provides a method of treating a bacterial infection in a pediatric patient wherein the formulation is administered in a dosage amount of 25 ± 10% mg/kg of amoxycillin and 3.6 ± 10% mg/kg of clavulanate in divided doses twice daily. In addition, the present invention includes a method of reducing the incidence of diarrhea associated with the treatment of a bacterial infection in a pediatric patient wherein the formulation is administered in a dosage amount of 45 ± 10% mg/kg of amoxycillin and 6.4 ± 10% mg/kg of clavulanate in divided doses twice daily. The common thread that runs through these claims is a dosage amount of amoxycillin and clavulanate in a ratio of 7:1 for administration to a pediatric patient in divided doses twice daily. Moreover, the specification demonstrates that the twice daily dosing schedules are as safe and effective as the previously known three times a day regimen at a 4:1 ratio (40/10mg/kg/day). This schedule unexpectedly achieves this efficacy with reduced side effects, and enhances compliance, all significant considerations in the pediatric patient.

In reaching its *prima facie* finding of obviousness, the Office seemingly combines various elements from the cited references without any clear suggestion from the references to do so. But without the motivation, such combinations are improper. As set forth in the M.P.E.P.:

> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

MPEP § 2143.01.

As described in previous responses, neither Rooke, WO 91/15197, nor GB 2005538A address methods of treatment, pediatric dosage amounts, dosage frequency, nor the decreased side effects as claimed in the present invention. The inventions focus on edible dessicants, a unit dose pharmaceutical composition (that does not include the specific 7:1 ratio as presently claimed), and effervescent couples, respectively. Without any teaching of pediatric doses (such as the claimed dosage amount of 45mg/kg/day, or any other dosage amount having a 7:1 ratio for children) none of these references can provide any motivation to combine, any reasonable expectation of success, or all the elements of the present claims.

The remaining references are similarly deficient but for different reasons. While Ruberto, Feldman, and Arguedas each disclose a method of, or a composition for, treating

infection in children, in each, the disclosure actually teaches away from the instant invention. And, of course, the prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention. MPEP 2141.02. Moreover, the Federal Circuit has repeatedly recognized that proceeding contrary to the accepted wisdom in the art represents "strong evidence of unobviouness." *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 10986). In each of these three references, the author points researchers in a different direction from the instant invention, thus negating any motivation to combine.

In Ruberto, the authors state that the side effects in two patients (5%) with gastralgia and vomiting, and three patients (7%) with abdominal pain and diarrhea were reduced by dividing the daily dose of amoxycillin-clavulanic acid into 8 hour rather than 12 hour intervals (p. 170, left column, last paragraph). An 8 hour dosage interval is the three-times-a-day dosage regimen of the prior art. Thus, this reference teaches away from the 12 hour, the "divided doses twice daily" of the present methods.

In Feldman, the authors compared the effectiveness of amoxicillin-clavulanate to trimethoprim-sulfamethoxazole in treating acute otitis media. First, this study used a ratio of amoxicillin to clavulanate of 4:1. As to the comparisons, the trimethoprim-sulfamethoxazole combination demonstrated a significantly higher rate of cure (*see* Abstract and Table 1), teaching away from the amoxicillin/clavulanate formula. In addition, the GI side effects with amoxicillin were significantly higher than the trimethoprim group, yielding the same teach away conclusion. Indeed, the authors noted that the eight cases of diarrhea severe enough to stop therapy were all in the amoxicillin-clavulanate group (p. 117, right column, third paragraph). Also, 93% of the infants with perianal and diaper rashes developed in the amoxicillin group (*id.*). The study concludes by expressly stating that "trimethoprim-sulfamethoxazole appears to be the most effective antibiotic." *See* p. 118, Conclusion. Thus, the study can not provide motivation to even use amoxicillin/clavulanate, let alone increase the amoxicillin ratio or dosage.

In Arguedas, the authors use amoxicillin/clavulanate simply as a comparison in their evaluation of "two attractive alternatives [cefprozil and loracarbef] for the management of patients with acute otitis media." *See* p. 317, last line. Moreover, the amoxicillin/clavulanate formulation used contained a 2:1 ratio of components. Thus, the reference provides no

motivation to even use an amoxicillin/clavulanate formulation, let alone the ratio or dosages presently claimed.

The Jacobsson reference also teaches away from the instant invention. It evaluated amoxicillin/clavulanate twice a day versus three times a day in the treatment of otitis media in children, but only at a 4:1 ratio (50 mg/ml amoxicillin and 12.5 mg/ml clavulanate given b.i.d. and 25 mg/ml amoxicillin and 6.25 mg/ml clavulanate given t.i.d. (p. 320, left column, last paragraph)), not the 7:1 amoxicillin/clavulanate of the of the present invention. The daily doses differed as well. The study gave between 26.6 and 33.2 mg of amoxicillin per kg body weight for the b.i.d. regimen and between 20.0 and 25.0 mg amoxicillin for the t.i.d. regimen *(id)*. In contrast, the amoxicillin dosages of the claimed inventions are 45 mg/kg/day and 25 mg/kg/day in a ratio of 7:1 amoxicillin to clavulanate given twice a day.

In comparing the side effects between the b.i.d. and t.i.d. groups, the authors note the rate of adverse events was higher in the b.i.d. group (p. 322, right col., first paragraph), but noted "this might be the result of the slightly higher daily in take in this study group (27-33 mg/kg) compared to the t.i.d. group (20-25 mg/kg)" (p. 323, right col., third paragraph). Although this difference in side effects was not statistically significant, a breakdown of the symptoms revealed that the b.i.d. group had nearly double the amount (13 out of 155 patients) of diarrhea as the t.i.d. group (7 out of 156 patients) (p. 322, Table 3).

By suggesting that the adverse side effects were related to the higher daily intake of amoxicillin per kg body weight, Jacobsson provides no motivation to increase the amoxicillin dose, as claimed in the current invention. Moreover, this focus on the amount of amoxicillin provides no motivation to change the ratio to decrease the (total) amount of clavulanate in order to reduce the incidence of diarrhea. The reference implies the side effects were related to the amoxicillin, not the clavulanate. Also, by finding that the 4:1 ratio was effective, the reference provides no further motivation to modify the ratio to 7:1. And, of course, the increased rate of diarrhea in the b.i.d. group teaches away from that dosage interval as a solution to the problem of diarrhea as a side effect when treating pediatric patients.

In conclusion, none of the these references provide a motivation to modify the prior art to arrive at the claimed invention. A *prima facie* case of obviousness cannot be established.

In the Office Actions dated November 3, 2000, and April 10, 2003, the Office states a basis for motivation, as follows: "one skilled in the art would be motivated to employ the 7:1

ratio for treating children in the absence of a side-by-side comparison over the prior art ratio." It appears that the Office is finding motivation in the lack of motivation to conduct a "side-by-side" comparison. Because this certainly cannot constitute a legally cognizable motivation to combine (indeed, it seems to counter any possible motivation), Applicants respectfully request clarification and explanation of this statement.

The Office also cites Behre, one of the clinical studies Applicants submitted in the prosecution of the parent case, as proof that "Applicant's remarks are insufficient in view of prior art test." Of course, the Behre et al paper is not prior art to the instant application. This application claims priority to its parent, USSN 08/945,365, which entered the U.S. national stage on January 9, 1998, and which was originally filed on May 2, 1996, as PCT /EP96/01881. The PCT claims the benefit of priority to GB 9508989.2 filed on May 3, 1995, and GB 9523655.0 filed on November 18, 1995. Behre was published in 1997. However, the underlying clinical trial reported in Behre is in fact, Clinical B in the present specification, page 6, lines 21 to end, and page 7.

In any event, the Office makes far too much of the lack of "statistically significant difference in incidence of adverse experiences between the two groups" [4:1 to 7:1]. It is true that Behre does conclude that there is no "statistical evidence" of a difference in "adverse experiences," (p. 165, left col., second paragraph), but those adverse experiences are bronchitis, rhinitis, and vomiting (*id.*). Instead, the focus should be on "bowel habit" which is discussed in the next section on page 165 of Behre. There, the authors state (as did Applicants upon the introduction of this paper in the parent case, Response filed Oct. 25, 1999, p. 5, paragraph 8) that:

> The proportion of patients with protocol defined diarrhoea was lower in the A/C b.i.d. group (6.7%) than in the A/C t.i.d. group (10.3%), although the difference was not statistically significant.

And although not "statistically significant," the importance of this finding is undeniable in light of its inclusion in the ultimate sentence of the conclusion:

> In conclusion, A/C given twice or three times daily was highly effective in the treatment of AOM in children. The two regimens showed equivalent clinical efficacy and both were well-tolerated, **with a lower incidence of protocol defined diarrhoea**. There was evidence of improved compliance with the b.i.d. regimen.

See p. 36.

The data in the specification (page 7, lines 21-23 also discuss this later point, " More patients in the BID group (81.3%) than in the TID group (72.8%) had at least 80% compliance over a 7-10 day treatment period [difference 10.3%; 95%CI (2.78%, 17.76%)]".

Other studies, including the clinical trial cited in the Physician's Desk Reference (PDR) 1998) of record, similarly focused on the incidence of diarrhea. Indeed, the PDR expressly recommends the 45 and 25 mg/kg/day 7:1 b.i.d. formulation over the 40 and 20 mg/kg/day 4:1 t.i.d. formulations because of decreased diarrhea, as follows:

> "The q12h regimen is recommended as it is associated with significantly less diarrhea (See CLINICAL STUDIES)".

See 1998 PDR (52nd Ed) at page 2801, center column, under Dosage and Administration for Patients aged 12 weeks and older, Footnote II II (enclosed and highlighted). It bases this recommendation on a study involving 575 pediatric patients which found that:

> The incidence of diarrhea was significantly lower in patients in the q12h treatment group compared to patients who received the q8h regimen (14.3% and 34.3%, respectively). In addition, the number of patients with either severe diarrhea or who were withdrawn with diarrhea was significantly lower in the q12h treatment group (3.1% and 7.6% for the q12h/10 and q8h/10 day, respectively).

See p. 2802, left column, under Clinical Studies (highlighted).

The ultimate conclusion of the clinical study described in the PDR is the same as the determination in Behre: that the clinical efficacy was "comparable." *Id.* Somehow, the Office sees in that a reason to question the non-obviousness of the invention. This is simply not correct. As Applicants indicated in the Oct. 25, 1999, response noted above:

> "Thus, the overall conclusion of the studies on the 7:1 formulations given twice daily is that they are as effective in treating infections, including acute otitis media and lower respiratory tract infections, as the original 4:1 formulations given three times daily. While these did not show superior efficacy (they were not designed that way), they did achieve neutral outcome, but it is not a "given" and has to be proven clinically to the satisfaction of regulatory bodies such as the FDA in order to allow registration of the new regimen. That it has, and with decreased side effects (an unexpected outcome)."

Applicants maintain that the Office's rejection of claims 32-49 under 35 U.S.C. §103 is improper and respectfully requests reconsideration and withdrawal of the outstanding rejection.

Conclusion

With the entry of this Amendment, claims 32-49 are pending. Applicants earnestly and respectfully request the Office to reconsider its finding of *prima facie* obviousness and allow the pending claims. Should this paper not result in a Notice of Allowance, Applicants respectfully request a formal interview with the Examiner prior to issuance of the next office action.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. It is not believed that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case, the Commissioner is hereby authorized to charge Deposit Account 19-2570 accordingly.

Date: October 10, 2003

Respectfully submitted,

Dara L. Dinner
Attorney for Applicants
Registration No. 33,680

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-5017
Facsimile (610) 270-5090
31167C1oa1.doc